

Biologics License Application 125197 Sipuleucel-T (APC8015)

Questions to sponsor:

1. Please summarize the procedure for determination of survival and determination of date of death. We note that in section 6.10 of the protocol; (Long Term Follow-Up) the following procedures were described: “The date and cause of death must be recorded in the source documentation. Death certificates should be obtained. If a death certificate cannot be obtained, verification of the date of death by the social security death index and/or the date and cause of death as recorded in a hospital discharge summary should be documented.”

2. For the following subjects the 9902B DEATH dataset does not contain any numerical entry in the DTHDYS (Days of survival). Please confirm the randomization and death dates and explain why survival times were not included in the dataset. Please clarify if these patients were excluded from the ITT primary analysis and, if so, please justify the exclusion.

Table 1

Subject ID	Randomization Date	DOD	DTHDYS
----(b)(6)----	07/29/2006	----(b)(6)----	
----(b)(6)----	09/18/2006	----(b)(6)----	
----(b)(6)----	11/14/2003	----(b)(6)----	
----(b)(6)----	01/26/2007	----(b)(6)----	
----(b)(6)----	03/09/2007	----(b)(6)----	
----(b)(6)----	03/23/2007	----(b)(6)----	
----(b)(6)----	09/24/2007	----(b)(6)----	
----(b)(6)----	07/25/2005	----(b)(6)----	
----(b)(6)----	04/26/2004	----(b)(6)----	
----(b)(6)----	11/23/2005	----(b)(6)----	

3. For the following subject an apparent discrepancy in date of randomization (DOR) between Investigator's determination in the CRF and dataset is noted. Please provide clarifications for these discrepancies:

Table 2

Subject ID	Dataset DOR	Investigator's DOR	Comments
----(b)(6)----	07/24/2006	06/30/06	
----(b)(6)----	07/12/2004	07/08/04	
----(b)(6)----	10/12/2006	10/11/06	
----(b)(6)----	07/16/2004	Not provided	
----(b)(6)----	09/24/2007	09/19/07	
----(b)(6)----	02/20/2004	Not provided	
----(b)(6)----	09/27/2004	09/24/04	
----(b)(6)----	07/13/2007	07/16/07	
----(b)(6)----	09/07/2006	09/06/06	
----(b)(6)----	01/25/2007	01/23/07	

4. For the following subject's the exact date of death was not documented in the CRFs. Please explain if the death date was imputed in the datasets and, if so, how this was done.

Table 3

Subject ID	Dataset DOD	Investigator's DOD	DC/SSDI DOD	Comments
---(b)(6)---	---(b)(6)---	---(b)(6)---	---(b)(6)---	
---(b)(6)---	---(b)(6)---	---(b)(6)---	Not provided	Per wife, exact date unknown
---(b)(6)---	---(b)(6)---	---(b)(6)---	Not provided	

5. The following subjects had deaths documented by Social Security Index by the DTHDTCNF column in the 9902B DEATH dataset however the SSI was not included in the CRF. Please provide a copy of the SSI or clarify why the death certificate or SSI or hospital records was not provided.

---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---

6. The following subjects had deaths documented by death certificates per the DTHDTCNF column in the 9902B DEATH dataset however we were not able to locate a copy in the CRF. Please provide a copy of the death certificate or clarify why the death certificate or SSI or hospital records confirming date of death cannot be provided.

---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---
 ---(b)(6)---

7. The following subject had death documented by obituary per the by the DTHDTCNF 9902B DEATH dataset however we were not able to locate the obituary in the CRF. Please confirm that the obituary was not submitted and, if so, clarify why it could not be provided. Also please confirm that SSI database was queried and that no information could be obtained and that a death certificate or hospital records confirming date of death could not be obtained.

---(b)(6)---

8. The following subjects had the date of death confirmed by the investigator based on an obituary. The obituary has been provided, however no death certificate or SSDI was located in the CRF. Please confirm that SSI database was queried and that no information could be obtained and that a death certificate could not be obtained, (per section 6.10 of the protocol).
 -----(b)(6)----- (Death Certificate is not available)

----- (b)(6) -----
----- (b)(6) -----
----- (b)(6) -----

8. The following subjects had a date of death documented by the PI but the FDA reviewer could not find corroborating information. Please confirm that SSI database was queried and that no information could be obtained and that no death certificate could be obtained, or provide documentation of date of death such as a death certificate or SSI or hospital records.

[illegible]